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Supporting Information

A Kinetic and Structural Investigation of DNA-Based Asymmetric Catalysis using the First Generation Ligands

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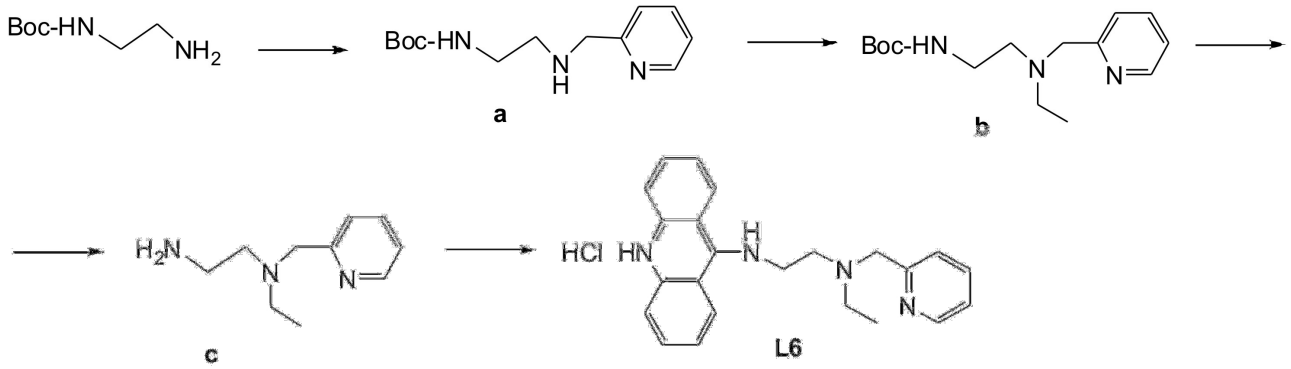
Synthesis of Ligand L6 (d)



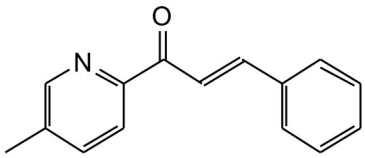
Reductive aminations: *tert*-butyl 3-[(2-pyridinylmethyl)amino]ethylcarbamate (a) [i]
Starting from mono-Boc protected ethylene diamine (1.00 g, 6.3 mmol) the pure product **a** a was obtained (2.19 g, 8.3 mmol) as slightly yellow oil.

Alkylations: *tert*-butyl 3-[(1-ethyl)(2-pyridinylmethyl)amino]ethylcarbamate (b)
A solution of the product *tert*-butyl 3-[(2-pyridinylmethyl)amino]ethylcarbamate (a) (1.05 g, 4.18 mmol), ethylbromide (0.59 g, 1.3 eq), K_2CO_3 (0.57 g, 4.18 mmol) in CH_3CN was placed under nitrogen. After heating under reflux for 16 h the solvent was evaporated and the crude material redissolved in water (30 ml). Extraction with ethyl acetate (3×20 ml) was followed by washing the combined organic layers with brine. After drying (Na_2SO_4) the ethyl acetate was evaporated and the crude material subjected to column chromatography (Alox, akt III, neutral, heptane: ethyl acetate: triethyl amine 20:10:1). The pure product **b** was obtained (1.36 g, 4.8 mmol) as a yellow oil.
^{1}H-NMR ($CDCl_3$, 400 MHz) *d* 8.59 (m, 1H), 7.70 (m, 1H), 7.45 (m, 1H), 7.21 (m, 1H), 5.32 (s, 1H, NH), 3.78 (s, 2H) 3.20 (m, 2H), 2.69 (m, 4H), 1.51 (s, 9H), 1.11 (t, *J*=7.03 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 400 MHz) *d* 12.41, 40.33, 48.82, 57.34, 60.78, 122.29, 123.24, 136.83, 149.47; HRMS= *m/z* (%): calcd 279.1947, found 279.1963.

Deprotection: N^1-(ethyl)-N^1-(2-pyridinylmethyl)-1,2-ethanediamine (c)
To a solution of *tert*-butyl 3-[(1-ethyl)(2-pyridinylmethyl)amino]ethylcarbamate (b) (1.36 g, 4.8 mmol) in CH_2Cl_2 (27 ml) was added thiophenol (2.95 ml, 0.028 mmol) and trifluoroacetic acid (2.95 ml, 0.04 mmol). After stirring for 6 h at room temperature aq. 1 M HCl solution (30 ml) was added. The CH_2Cl_2 was evaporated and the aqueous layer was extracted with diethyl ether (3×70 ml). The pH of the aqueous phase was brought to >10 by addition of aq. 2 M NaOH. Extraction with CH_2Cl_2 (3×30 ml) was followed by washing of the combined organic layers with brine. After drying the solvent was removed in vacuo to give the pure product **c** (0.930 g, 5.1 mmol) as yellow oil.
^{1}H-NMR ($CDCl_3$, 400 MHz) *d* 8.62 (d, *J*=4.83 Hz, 1H), 7.66 (m, 1H), 7.47 (s, 1H), 7.16 (m, 1H), 3.84 (s, 2H), 2.82 (m, 4H), 2.64 (m, 2H), 1.41 (s, 2H), 1.12 (t, *J*=7.10 Hz, 3H); HRMS= m/z (%): calcd 179.1422, found 179.1426.

Coupling to acridine: N^1-(9-acridinyl)-N^3-(1ethyl)-N^3-2-pyridinylmethyl)-1,3-ethanediamine (d)
A mixture of N^1-(ethyl)-N^1-(2-pyridinylmethyl)-1,2-ethanediamine (c) (0.28 g, 1.6 mmol), 9-chloroacridine (0.34 g, 1 eq) and phenol (1.71 g, 0.018 mmol) was placed under nitrogen and heated at 100 °C for 2h. After cooling to room temperature diethyl ether (50 ml) was added and the mixture was stirred for 1h. The diethyl ether was decanted from the dark oil, and fresh diethyl ether (50 ml) was added. After stirring for 2 d the hydrochloride salt of **d** (0.26, 1.45 mmol) as isolated as a yellow solid. Dissolving a small amount in aq. 1 M NaOH, followed by extraction with CH_2Cl_2 gave the free base as a dark yellow oil, which was used for characterization.
^{1}H-NMR ($CDCl_3$, 400 MHz) *d* 8.56 (m, 1H), 8.25 (d, *J*=8.56 Hz, 2H), 8.08 (d, *J*=8.20 Hz, 2H), 7.68 (m, 1H), 7.40 (m, 1H), 7.17 (m, 1H) 5.32 (s, 1H, NH), 3.91 (m, 2H), 2.95 (m, 2H), 2.80 (m, 2H), 1.26 (s, 2H), 1.17 (m, 3H); HRMS= m/z (%): calcd 356.2001, found 356.1999.

Synthesis Substrates:



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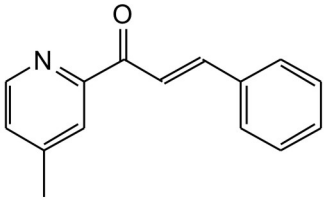

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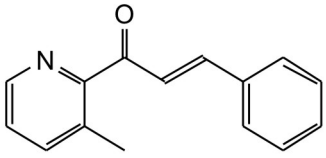

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2-Acetyl-5-methylpyridine and 2-Acetyl-3-methylpyridine were prepared following literature procedures.[ii] 2-Acetyl-4-methylpyridine was obtained from Sigma.

(E)-1-(5-methyl-2-pyridinyl)-3-phenyl-2-propen-1-one (4).

Starting from 2-acetyl-5-methylpyridine (0.55 g, 4.07 mmol), 0.54 g (2.44 mmol) of product were obtained, after chromatography on silica gel (Pentane/AcOEt 10:1) as yellow solid. Mp 72.5-81.4 °C; ^{1}H NMR (400 MHz,$CDCl_3$) *d* 8.56 (s,1H), 8.32 (d, *J*=16.04 Hz, 1H), 8.11 (d, *J*=7.98 Hz, 1H), 7.94 (d, *J*=16.07 Hz, 1H), 7.74 (m, 2H), 7.67 (m, 1H), 7.42 (m, 3H), 2.48 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) *d* 190.80, 152.75, 150.84, 145.29, 139.17, 136.31, 131.91, 130.00, 134.07, 122.16, 19.87. HRMS= *m/z* (%): calcd 223.09970; found 223.0999; elemental analysis calcd (%) for $C_{15}H_{14}ON$: C, 80.69; H, 5.87; N, 6.27; found: C, 80.69; H, 5.85; N, 6.32.

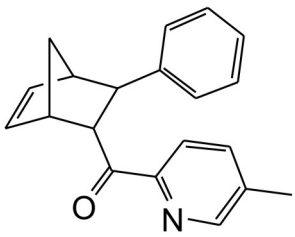
(E)-1-(4-methyl-2-pyridinyl)-3-phenyl-2-propen-1-one (5).

Starting from 1 g (7.4 mmol) of 2-Acetyl-4-methylpyridine, 1.32 g (5.92 mmol) of product were obtained, after purification on silica gel (Pentane/AcOEt 10:1) as yellow solid. Mp 100.9.2-101.0 °C; ^{1}H NMR (400 MHz,$CDCl_3$) *d* 8.61 (d,1H, *J*=4.88 Hz), 8.32 (d, 1H, *J*=16.05), 8.03 (m, 1H), 7.96 (d, 1H, *J*=16.05), 7.74 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 2.35 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) *d* 190.62, 155.21, 149.62, 146.08, 136.57, 131.35, 130.23, 128.55, 124.46, 122.04, 23.26. [M^+]: calcd 224.10692; found 224.10692. elemental analysis calcd (%) for $C_{15}H_{13}ON$: C, 80.69; H, 5.87; N, 6.27; found: C, 80.56; H, 5.86; N, 6.21.

(E)-1-(3-methyl-2-pyridinyl)-3-phenyl-2-propen-1-one (6).

Starting from 0.87 g (6.5 mmol) of 2-Acetyl-3-methylpyridine, 1.07 g (4.8 mmol) of product were obtained, after chromatography on silica gel (Pentane/AcOEt 10:1) and recrystallisation as yellow solid. Mp: 78.7-79.0°C; ^{1}H NMR (400 MHz,$CDCl_3$) *d* 8.55 (s,1H), 8.00 (d, *J*=16.09 Hz, 1H), 7.79 (d, *J*=16.01 Hz, 1H), 7.67 (m, 2H), 7.60 (m, 1H), 7.40 (m, 3H), 7.33 (m, 1H), 2.69 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) *d* 192.28, 153.19, 146.36, 144.49, 140.16, 135.31, 130.61, 129.01, 125.90, 124.20, 20.20; HRMS= *m/z* (%): calcd 223.09970; found 223.10017. elemental analysis calcd (%) for $C_{15}H_{14}ON$: C, 80.69; H, 5.87; N, 6.27; found: C, 80.48; H, 5.87; N, 6.31.

Diels-Alder products (major, endo isomer):



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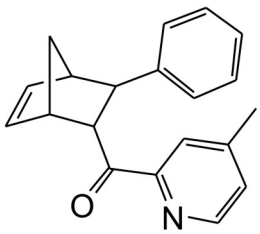

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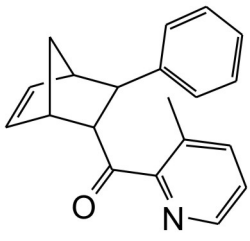

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(5-methyl-2-pyridinyl)(3-phenylbicyclo[2.2.1]hept-5-en-2-yl)methanone (7).

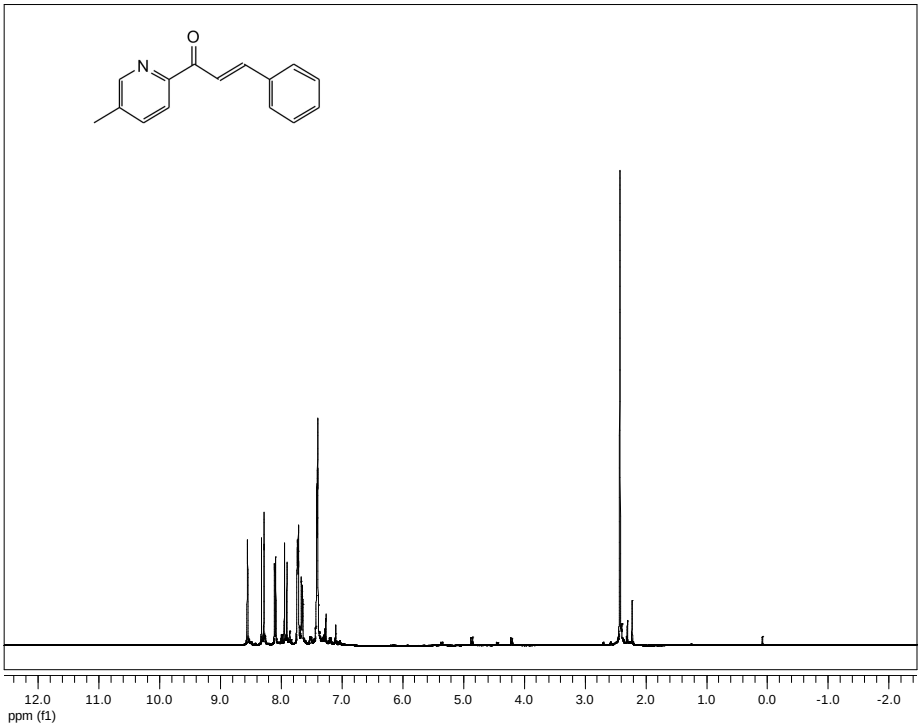
^{1}H NMR (400 MHz,$CDCl_3$) *d* 8.52 (s, 1H), 7.97 (d, *J*=7.85 Hz, 1H), 7.65 (d, *J*=7.82 Hz, 1H), 7.38 (m, 5H), 6.50 (s, 1H), 4.56 (m, 1H), 3.57 (m, 1H), 3.10 (s, 1H), 2.49 (s, 3H), 2.08 (d, J= 8.36 Hz, 1H), 1.6 (d, J= 8.16 Hz, 1H); HRMS= m/z (%): calcd 289.1467, found 289.1461.

(4-methyl-2-pyridinyl)(3-phenylbicyclo[2.2.1]hept-5-en-2-yl)methanone (8).

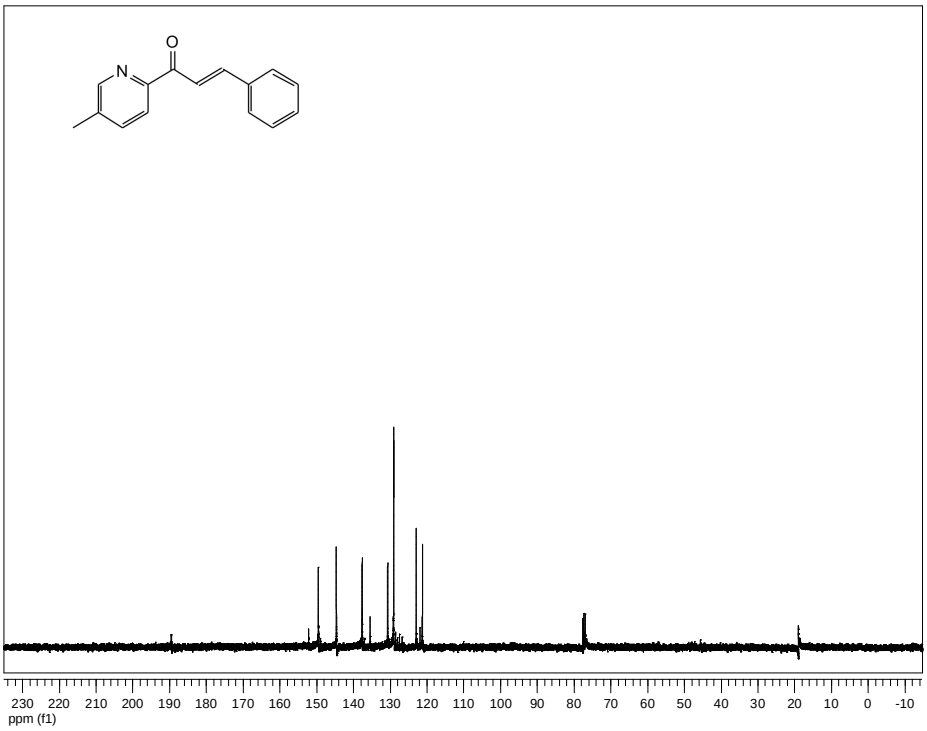
^{1}H NMR (400 MHz,$CDCl_3$) *d* 8.56 (d, *J*= 4.86 Hz, 1H), 7.85 (s, 1H), 7.35 (m, 5H), 6.51 (m,1H), 5.84 (m, 1H), 4.56 (m,1H), 3.57 (s, 1H), 3.44 (d, *J*=4.25 Hz, 1H), 3.11 (s, 1H), 2.44 (s, 3H), 2.10 (d, *J*=8.10, 1H), 1.63 (d, *J*=9.94 Hz, 1H); HRMS= m/z (%): calcd 289.1467, found 289.1474.

(3-methyl-2-pyridinyl)(3-phenylbicyclo[2.2.1]hept-5-en-2-yl)methanone (9).
^{1}H NMR (400 MHz,$CDCl_3$) *d* 8.53 (d, *J*= 4.59 Hz, 1H), 7.58 (d, *J*= 7.75 Hz, 1H), 7.34 (m, 6H), 5.94 (m, 1H), 4.55 (m, 1H), 3.35 (d, *J*= 3.81 Hz, 2H), 3.42 (s, 1H), 3.08 (s, 1H), 2.49 (s, 3H), 1.98 (d, *J*=8.44 Hz, 1H), 1.55 (dd, *J*= 1.71 Hz, *J*= 8.48 Hz, 1H); HRMS= m/z (%): calcd 289.1467, found 289.1463.

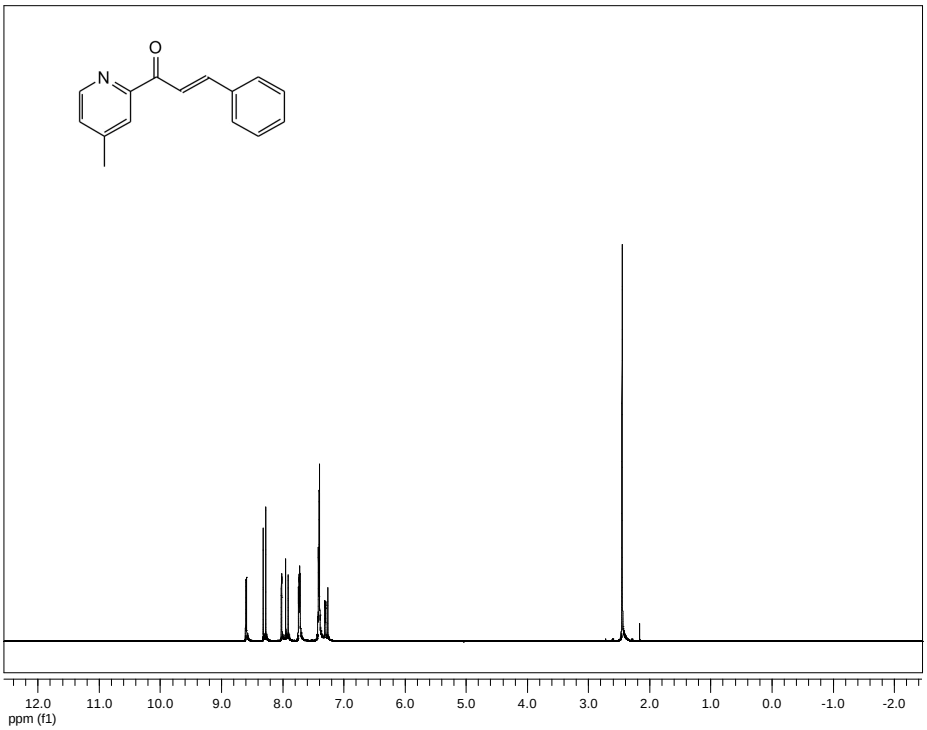
4 ^{1}H-NMR



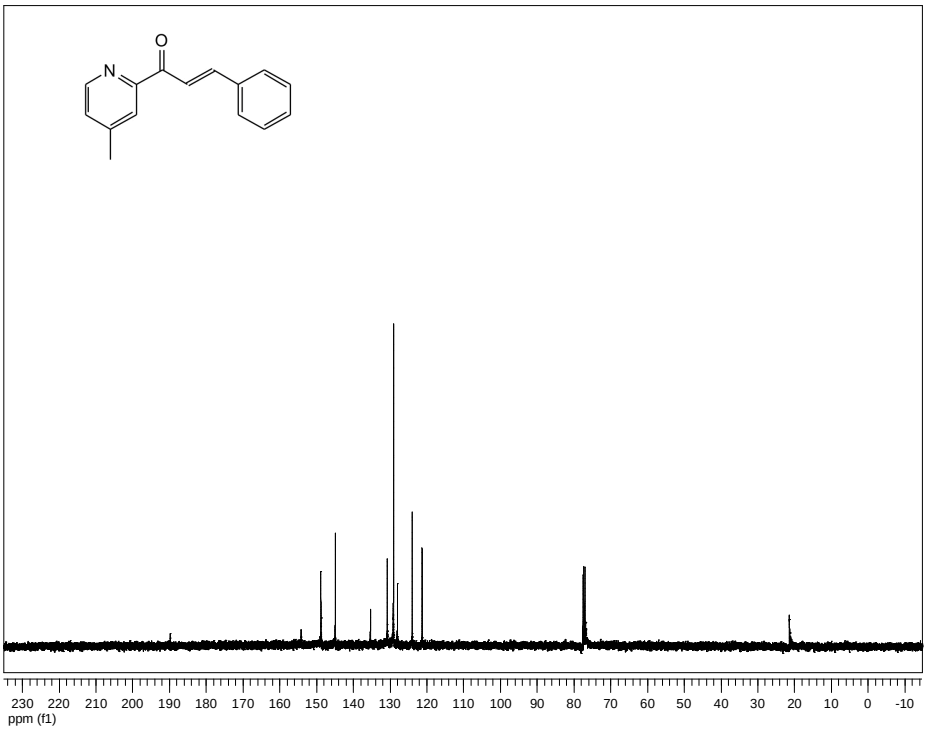
4 ^{13}C-NMR



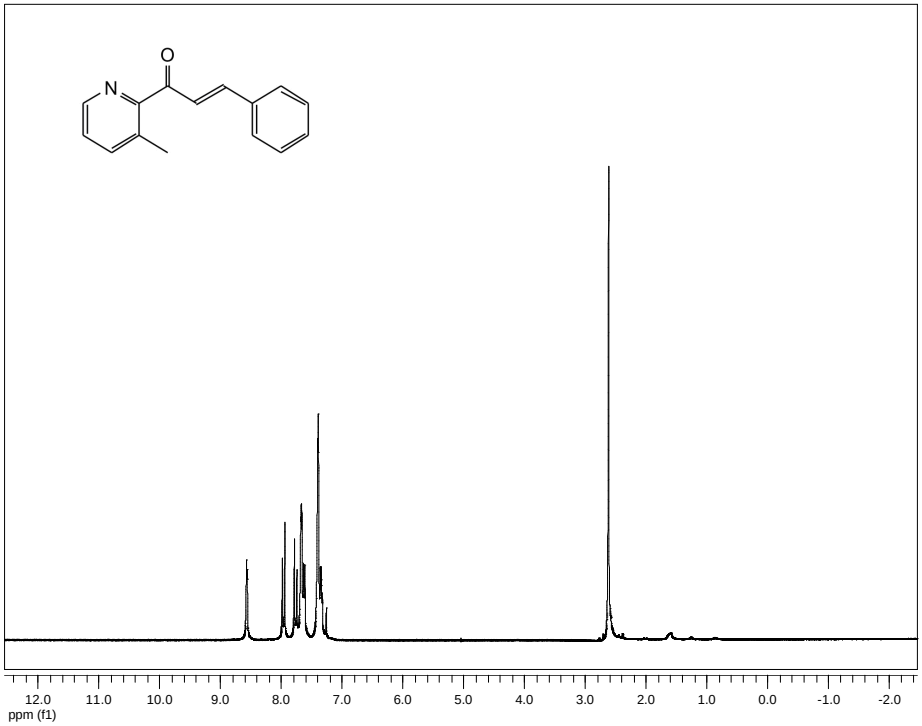
5 ^{1}H-NMR



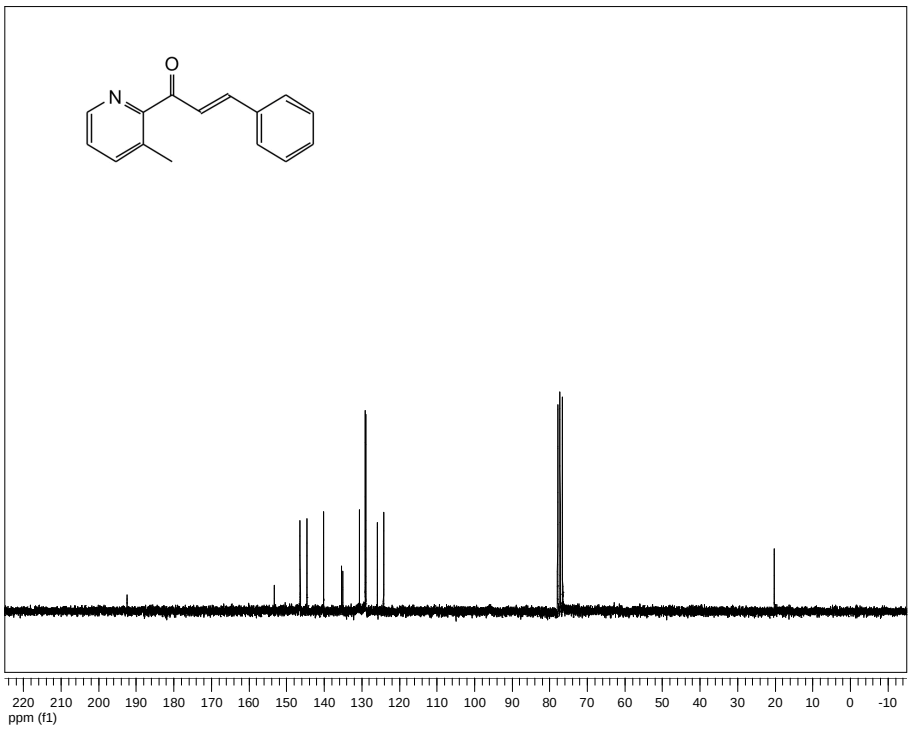
5 ^{13}C-NMR



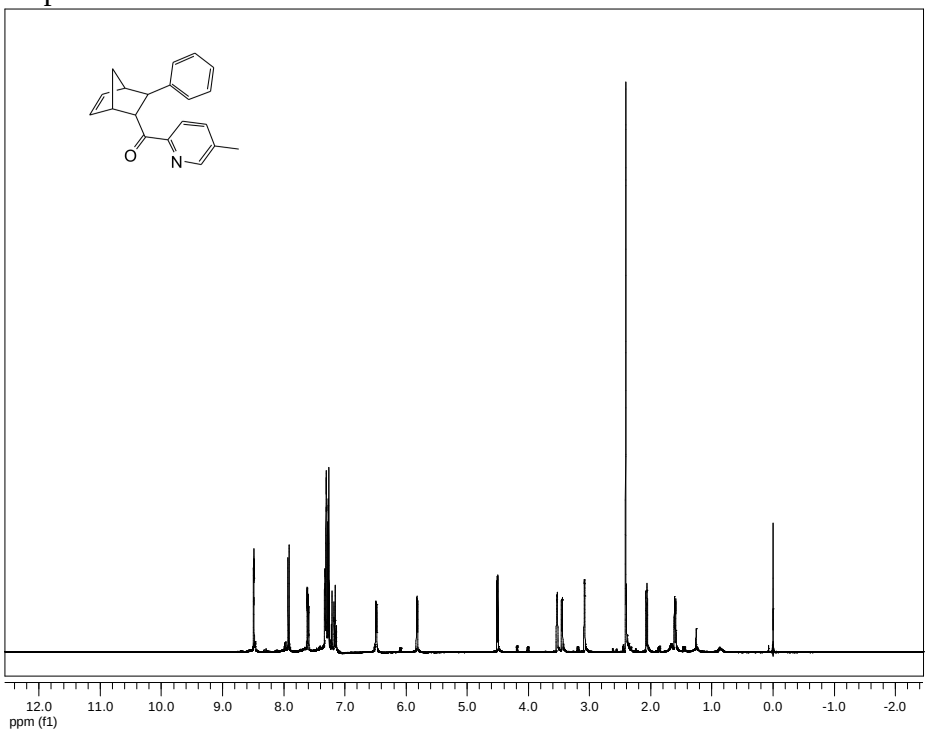
6 ^{1}H-NMR



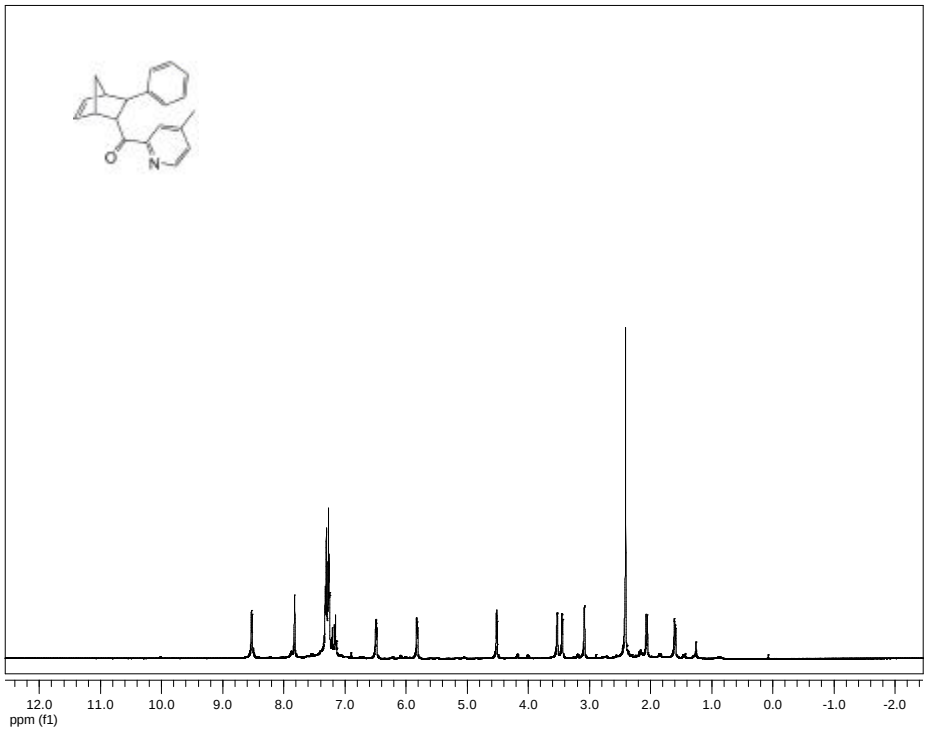
6 ^{13}C-NMR



Diels-Alder product **7**



Diels-Alder product **8**



Diels-Alder product **9**

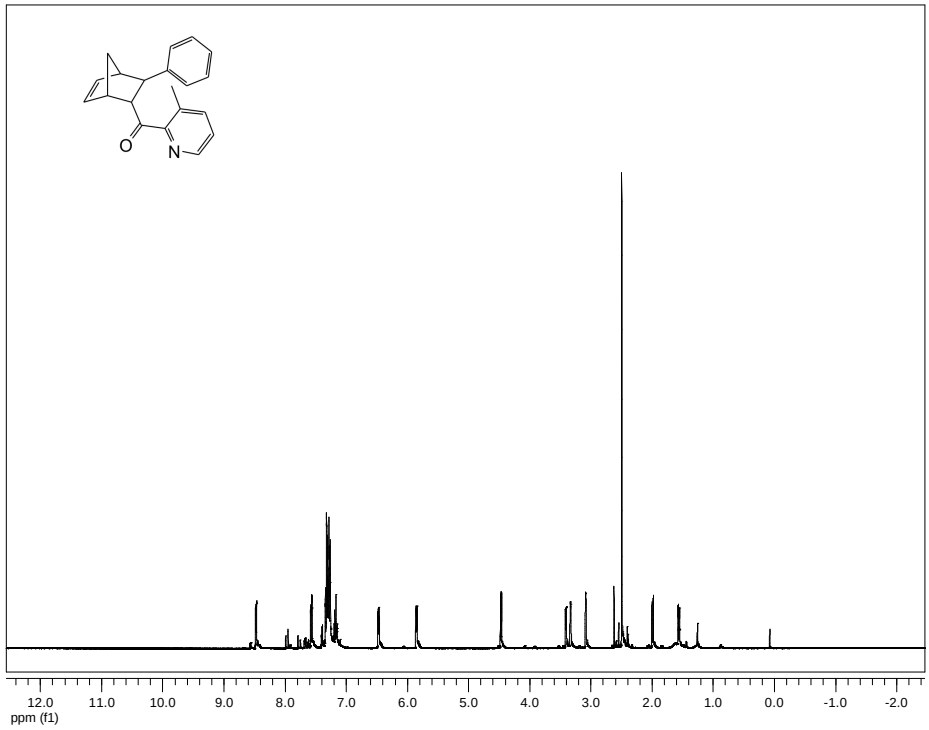


Table S1. Dependence of enantioselectivity on the pH. [a]

entry	ligand	pH	buffer	conversion [%]	ee endo[b] [%]
1	L1	6.5	MOPS	>80	-37
2	L1	5.5	MES	100	-38
3	L2	6.5	MOPS	100	-37
4	L2	5.5	MES	100	-35
5	L3	6.5	MOPS	100	-48
6	L3	5.5	MES	100	-34
7	L4	6.5	MOPS	100	49
8	L4	5.5	MES	100	32

[a] Conditions: all experiments were carried out with st-DNA (1.3 mg mL^{-1}) $[Cu(L)(NO_3)_2]$= 0.3 mM; [**1**]=1 mM; [**2**]=15 mM in buffer (20 mM) for 3 d at 5°C. Conversion was determined by ^{1}H-NMR, the ee was determined by chiral HPLC: ODH column *n*-heptane/*i*-PrOH 98:2, 0.5 ml/min; OD column *n*-heptane/*i*-PrOH 98:2, 1 ml/min. [b] +/- are referring to the order of elution of the two enantiomers: first and second, respectively. Retention times: 13.7 min and 16.06 min (endo isomer; ODH); 7.2 min and 8.3 min (OD; endo isomer).

Synthesis and crystallisation Cu-L1 complex for X- ray study:
Crystallisation from a mixture acetonitrile and acetyl acetate. (0.14 mmol, 67 mg) *N*1-(9-acridinyl)-*N*3-(3,5-dimethoxybenzyl)-*N*3-2-pyridinylmethyl)-1,3-ethanediamine (L1), was added to 20 mg (0.2 mmol) of $HClO_4$ in MeOH (1.5 ml) and then 1.1 eq (57 mg) of $Cu(ClO_4)_2 \cdot 6H_2O$ in CH_3CN (1.5 ml) was added. The resulting solution was placed in an EtOAc bath. After 3 d, the supernatant was removed and the solid was redissoved in 7 mL of CH_3CN and placed in an AcOEt bath. Fragile platelet shaped green colored crystals were obtained suitable for X-Ray analysis.
X-ray diffraction: Crystal and Molecular Structure.
Although an X-ray structure determination was thwarted by persistent weak scattering power of the crystals, and deterioration of the lattice probably due to loss of solvent from the crystal lattice during the preparation and mounting of the crystal before it was transferred into the cold nitrogen stream. Ultimately there was found a crystal fit to the X-ray experiment.
A crystal with the dimensions of 0.33 x 0.20 x 0.08 mm was mounted on top of a glass fiber, and aligned on a Bruker. SMART APEX CCD diffractometer (Platform with full three-circle goniometer). The diffractometer was equipped with a 4K CCD detector set 60.0 mm from the crystal. The crystal was cooled to 100(1) K using the Bruker KRYOFLEX low-temperature device. Intensity measurements were performed using graphite monochromated M_o-K$\overline{a}$ radiation from a sealed ceramic diffraction tube (SIEMENS). Generator settings were 50 KV/ 40 mA. SMART was used for preliminary determination of the unit cell constants and data collection control. The intensities of reflections of a hemisphere were collected by a combination of 3 sets of exposures (frames). Each set had a different ϕ angle for the crystal and each exposure covered a range of 0.3° in ω. A total of 1800 frames were collected with an exposure time of 10.0 seconds per frame. The overall data collection time was 8.0 h. Data integration and global cell refinement was performed with the program SAINT. The final unit cell was obtained from the xyz centroids of 7360 reflections after integration. Intensity data were corrected for Lorentz and polarization effects, scale variation, for decay and absorption: a multi-scan absorption correction was applied, based on the intensities of symmetry-related reflections measured at different angular settings (SADABS) and reduced to F_o^2. The program suite SHELXTL was used for space group determination (XPREP).
The unit cell. was identified as triclinic. Reduced cell calculations did not indicate any higher metric lattice symmetry. Space group, P-1, was determined from considerations of the unit cell parameters, statistical analyses of intensity distributions: the E-statistics were indicative of a centrosymmetric space group. Examination of the final atomic coordinates of the structure did not yield extra crystallographic or metric symmetry elements.
The structure was solved by Patterson methods and extension of the model was accomplished by direct methods applied to difference structure factors using the program DIRDIF. The positional and anisotropic displacement parameters for the non-hydrogen atoms were refined. Some atoms showed unrealistic displacement parameters when allowed to vary anisotropically, suggesting dynamic disorder (dynamic means that the smeared electron density is due to fluctuations of the atomic positions within each unit cell), especially some oxygen position of the perchlorate ions. This is in line with the weak scattering power of the crystals investigated.
Refinement was frustrated by a disorder problem: from the solution it was clear that one acetonitrile solvent molecule was highly disordered: the electron density of the atoms appeared to be spread out, indicating positional disorder. No satisfactory discrete model could be fitted in this density. The BYPASS procedure was used to squeeze out the disordered acetonitrile solvent molecule (residue 5).
Hydrogen atoms were constrained to idealized geometries and allowed to ride on their carrier atoms with an isotropic displacement parameter related to the equivalent displacement parameter of their carrier atoms, except the hydrogen atoms of the water ligand which is coordinated to the nuclear Cu atom of residue 2.
Final refinement on F^2 carried out by full-matrix least-squares techniques converged at $wR(F^2) = 0.1735$ for 15289 reflections and $R(F) = 0.0690$ for 8551 reflections with $F_o \geq 4.0\ \sigma(F_o)$ and 1153 parameters. The final difference Fourier map was essentially featureless: no significant peaks (1.2(1) e/Å^3; in the neighborhood of C91) having chemical meaning above the general background were observed.
The positional and anisotropic displacement parameters for the non-hydrogen atoms and isotropic displacement parameters for hydrogen atoms were refined on F^2 with full-matrix least-squares procedures minimizing the function $Q = \sum h[w(|(F_o^2) - k(F_c^2)|)^2]$, where $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, $P = [\max(F_o^2,0) + 2F_c^2] / 3$, F_0 and Fc are the observed and calculated structure factor amplitudes, respectively; ultimately the suggested a (=0.082) and b (=0.0) were used in the final refinement.
Neutral atom scattering factors and anomalous dispersion corrections were taken from International Tables for Crystallography. All refinement calculations and graphics were performed on a HP XW620 (Intel XEON 3.2 Ghz) / Debian-Linux computer at the University of Groningen with the program packages SHELXL (least-square refinements), a locally modified version of the program PLATON package.

References

i) G. Roelfes, B. L. Feringa, *Angew. Chem.-Int. Ed.*, **2005**, *44*, 3230-3232.

ii) M. Hatanaka, K. Takahashi, S. Nakamura, T. Mashino, *Bioorg. Med. Chem.*, **2005**, *13*(24), 6763-6770.